UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/692,563	10/24/2003	Michael Draper	16534-526002US	9127

30623 7590 03/04/2009

MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
QAZI, SABIHA NAIM	

ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
03/04/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/692,563	DRAPER ET AL.	
	Examiner	Art Unit	
	Sabiha Qazi	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,29-36,42,43,49-62,66-82,84 and 85* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,29-36,42,43,49-62,66-82,84 and 85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/19/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Non-Final Office Action

Claims 1, 3-4, 29-36, 42-43, 49-62, 66-82 and 84-85 are pending. No claim is allowed. Amendments are entered.

Summary of the Office Action dated 02/27/2009

1. Information Disclosure Statement
2. Copending Applications
3. Specification
4. 35 USC § 112(1) Written Description Rejection
5. 35 USC § 112(1) Scope of Enablement Rejection
6. Double Patenting Rejections
7. Response to Remarks
8. Communication

Applicants' arguments, filed on 12/05/2008 have been fully considered. Rejections not reiterated from previous office actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Information Disclosure Statement

The IDS filed on 12/19/2008 is duplicated of IDS filed on 12/12/2008.

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Copending Applications

Applicants must bring to the attention of the examiner, or other Office official involved with the examination of a particular application, information within their knowledge as to other copending United States applications, which are

"material to patentability" of the application in question. MPEP 2001.06(b). See Dayco Products Inc. v. Total Containment Inc., 66 USPQ2d 1801 (CA FC 2003).

Specification

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112—Written Description Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-4, 29-36, 42-43, 49-62, 66-82 and 84-85 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Following reasons apply: The prodrug moiety as in claims does not contain written description requirement.

The prodrug as defined in specification is complex and may include thousands of known and unknown compounds. See [0124] where prodrug are defined as "The term "prodrug moiety" includes moieties which can be metabolized in vivo to an active group and moieties which may advantageously remain attached in vivo. Preferably, the prodrug moieties are metabolized in vivo by enzymes, e.g., esterases or by other mechanisms to hydroxyl groups or other advantageous groups. Examples of prodrug and their uses are well known in the art (See, e.g., Berge et al. (1977) "Pharmaceutical Salts", J. Pharm. Sci. 66:1-19). The prodrug can be prepared in situ during the final isolation and purification of the compounds, or by separately reacting the purified compound with a suitable agent. Hydroxyl groups can be converted into esters via treatment with a carboxylic acid. Examples of prodrug moieties include substituted and unsubstituted, branch or unbranched lower alkyl ester moieties, (e.g., propionoic acid esters), lower alkenyl esters, di-lower alkyl-amino lower-alkyl esters (e.g., dimethylaminoethyl ester), acylamino lower alkyl esters (e.g., acetyloxymethyl ester), acyloxy lower alkyl esters (e.g., pivaloyloxymethyl ester), aryl esters (phenyl ester), aryl-lower alkyl

esters (e.g., benzyl ester), substituted (e.g., with methyl, halo, or methoxy substituents) aryl and aryl-lower alkyl esters, amides, lower-alkyl amides, di-lower alkyl amides, and hydroxy amides. Preferred prodrug moieties are propionoic acid esters and acyl esters". The definition is considered too broad and it appears that Applicant has no possession of the invention as has been claimed.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See, e.g., In re Wilder, 22 USPQ 369, 372-3 (Fed. Cir. 1984). (Holding that a claim was not adequately described because the specification did 'little more than outline goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.')

Mere indistinct terms such as "prodrug moiety", however, may not suffice to meet the written description requirement. This is particularly true when a compound is claimed in purely functional terms. See Univ. of Rochester v. G.D. Searle, 69 USPQ2d 1886 (CAFC 2004) at 1892, stating:

> The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. A description of an anti-inflammatory steroid, i.e., a steroid (a generic

> structural term) described even in terms of its functioning of lessening inflammation of tissues fails to distinguish any steroid from others having the same activity or function. A description of what a material does, rather than of what it is, usually does not suffice.... The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. (Emphasis added).

Conversely, a description of a chemical genus will usually comprise a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. See Univ. of Calf. V. Eli Lilly, 43 USPQ 2d 1398, 1406 (Fed. Cir. 1997). This is analogous to enablement of a genus under Section 112, ¶ 1, by showing the enablement of a representative number of species within the genus.

A chemical genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. *If the genus has substantial variance, the disclosure must describe a sufficient number of species to reflect the variation within that genus*. See MPEP 2163. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been

furnished in the disclosure of the Application. These include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any *combination of such identifying characteristics that distinguish the claimed invention from other materials* and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. MPEP 2163.

Here, the specification does not provide a reasonably representative disclosure a potentially huge genus inclusive of many different compounds having widely divergent structures and functions. Specifically, the specification discloses only a limited number of species at page and these are not viewed as being reasonably representative of the genus in its claimed scope because no readily apparent combination of identifying characteristics is provided, other than the disclosure of those specific species as examples of the claimed genus.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1, 3-4, 29-36, 42-43, 49-62, 66-82 and 84-85 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compounds when R7 can be furanyl, benzofuran and pyrrole group does not reasonable enabled for the large Markush of substituents which includes heterocyclic groups at various positions of tetracycline ring. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The specification discloses the compounds where aryl and alkylamino, heteroaromatic substituents can be at at various positions of tetracyclic ring. All these substituents contain large number of hetrocyclic substituents as has been defined in the disclosure. See lines 33-38 on page 10. There is no guidance and/or description of the large number of compounds to prepare and use them.

In claim 1 R2, R2', R4', and R4" are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, **alkylamino, arylalkyl, aryl,** heterocyclic, heteroaromatic or a prodrug moiety;
R 4 is NR4'R4", alkyl, alkenyl, alkynyl, hydroxyl, halogen, or hydrogen; Rs is hydroxyl, hydrogen, thiol, alkanoyl, **aroyl,** alkaroyl, **aryl, heteroaromatic**, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, **alkylamino**, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

The level of predictability in the art: There is no guidance in the specification how to make and use the invention of the compounds of formula (1) when aryl group can be a large number of hetero and non hetero groups as cited in specification on page 87, lines 5-26, gall hetero groups can be a large Markush group.

The synthesis of such a large variety of compounds having different structures and so different chemical properties cannot be predicted. Even when similar starting materials are used under the same conditions the products obtained are different.

As stated in the preface to a recent treatise:

"Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research

chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor- intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work..... Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too

copious)". Dorwald F. A. Side Reactions in Organic Synthesis, 2005, Wiley: VCH, Weinheim pg. IX of Preface (reference enclosed).

Thus synthesis of these compounds of the compounds of formula I containing heterocyclic groups as cited above is unpredictable.

The amount of direction provided by the inventor: The inventor provides very little direction in the instant specification. Only limited substituents on the compounds are made and disclosed. There is no preparation of compounds of formula (1) when wide range of 5-7 membered saturated or unsaturated ring heterocyclic rings which may contain a heteroatom selected from the group consisting of oxygen and nitrogen as a ring-forming atom. The availability of the starting material that is needed to prepare the invention as claimed is also at issue here. As per MPEP 2164.01 (b): A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. The Court in In re Ghiron, 442 F.2d 985,991,169 USPQ 723,727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can

be said if certain chemicals are required to make a compound or practice a chemical process. In re Howarth, 654 F.2d 103, 105,210 USPQ 689, 691 (CCPA 1981). There are no starting materials provided with respect to the various substituents at various positions of tetracyclic ring.

The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for practicing the claimed invention in its "full scope". No reasonable specific guidance is provided. The instant specification does not have any working examples with respect to the various substituents as given above. The state of the art indicates that even when the reactants are similar, and the reaction conditions are the same, it is not necessary that it would form the same products.

Presently claimed invention is drawn method of use of tetracycline compounds which include a large number of compounds substituted by various Markush groups at various positions.

The instant disclosure provides no evidence to suggest that this unit dose as

claimed can be extrapolated to tumors having unrelated mechanisms of resistance, and thus does not meet the "how to use" prong of 35 USC 112, first paragraph with regard thereto.

The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed compounds could be predictably made and use as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the claimed invention in its "full scope" a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Double Patenting Rejection

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1, 3-4, 29-36, 42-43, 49-62, 66-82 and 84-85 provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 165 of copending Application No. 10/835,635. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d

937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 1, 3-4, 29-36, 42-43, 49-62, 66-82 and 84-85 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 165 and 184.of copending Application No.10/853,635, claims 109 and 115 of 10/996,119 and claims 1-5 of 12/351,409. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims of the copending application are drawn to tetracyclines when R9 is hydrogen and R7 can be heterocyclic group, See compounds of formula (I) in claim 1 where same invention has been presently claimed.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Instant claims differ from the reference in that they are of different generic scope. It had been held by Courts that the indiscriminate selection of "some" from among "many" is considered prima facie obvious. In re Lemin, 141 USPQ 814 (1964); National Distillers and Chem. Corp. V. Brenner, 156 USPQ 163.
R7 is defind as furanyl, benzofuranyl, thienyl, benzothienyl, indolyl, or pyrrolyl

The instant claimed compounds would have been obvious because one skilled in the art would have been motivated to prepare compounds embraced by the genus of the above cited references with the expectation of obtaining additional beneficial compounds. The instant claimed compounds would have been suggested to one skilled in the art.

One having ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole. It has been held that a prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species falling within the genus. In re Susi, 440 F.2d 442, 445, 169 USPQ 423,

425 (CCPA 1971), followed by the Federal Circuit in Merck & Co. V. Biocraft Laboratories, 874 F.2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir. 1989).

1. Claims 1, 3-4, 29-36, 42-43, 49-62, 66-82 and 84-85 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-28 of copending Application No. 11/490,867. Although the conflicting claims are not identical, they are not patentably distinct from each other because R9 in copending application can be hydrogen and R7 can be aminoalkyl, alkylamino, aryl or heterocyclic moiety which has been claimed in the present application. Therefore, presently claimed invention is considered obvious to the claimed subject matter of the above co-pending application.

2. Claims of the present invention are generically taught by the prior art and are considered obvious for the reasons cited above.

Claims provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over 12/351,409 (claims 1-5, see claim 1 when R9 is H and R7 can be heterocyclic group), 10/921,580 (claims 1-20, see compound having benzofuran in claim 20); 10/943,571; 10/996,119; 11/039,230 (see claims 1, 32-35, 37-47).;11/348,608; 11/490,867. Although the conflicting claims are not identical, they are not patentably distinct from each other because

each encompasses 9-aminomethyl tetracycline compounds as defined by the instant claims. Presently claimed invention is broad and covers the compounds of the cited co-pending application when R9 represents alkylamino group. However, the claimed compounds and/or the 9- aminomethyl groups recited by the instant claims are encompassed by the claims of the cited copending applications.

Aryl, heteroaromatic, amino alkyl and heterocyclic groups as claimed group as defined in the specification represents large number of substituents which overlaps with several copending applications. In view of large number of copending applicants and issued patents it is not possible to go through each of them, for the same reason Applicant is requested to point out most relevant Application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Remarks

Applicant's election of group I is hereby acknowledged. A request to combine group III and XVII has been considered and these groups will be joined with the elected group I when from claims other heterocyclic and Markush groups

will be deleted. Compounds containing pyrrole are completely different from the compounds containing a furan ring. They are patentably distinct. Claims 1, 3-4, 29-30, 32-33, 36, 42-43, 49-62, 66-82 and 84-85 read on the elected species. Elected species is compound II from Table 2

Restriction is made final. Elected species is substituted however; the definition of R7 in claim 1 does not allow any substitution.

Application of Art to Non-Elected Species

Examination of claims for purposes other than application of prior art, e.g. rejections under 35 USC 112, first and second paragraphs, will be understood to be made in the interest of completeness of prosecution and should not be considered as indicating that search has been extended to non-elected species.

Communication

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sabiha Qazi whose telephone number is (571) 272-0622. The examiner can normally be reached on any business day except Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The

fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sabiha Qazi/

Primary Examiner, Art Unit 1612